II. REMARKS

Preliminary Remarks:

Current Status of the claims

Claims 2, 30, and 32-34 are amended herein, and claims 1, 4, 6-15, 22, 28, 29 and 31 stand canceled. Therefore, claims 2, 3, 5, 16-21, 23-27, 30 and 32-38 are currently pending.

Claim 2 is amended by labeling the individual steps of the method as steps (a)-(f), and by amending step (d) to specify assaying *in vitro* to identify soluble anti-human gp39 antibodies that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured with immobilized anti-CD3 antibodies, as described in the specification, *e.g.*, on page 36, lines 1-15, and Examples 18-21 (*e.g.*, *see* page 54, lines 19-23; page 56, lines 16-17; and page 57, lines 7-10).

Claims 30 and 33 are amended to refer to step (d) of claim 2 and to specify that the anti-human gp39 antibodies of the assay are soluble anti-human gp39 antibodies; and claims 30 and 32-34 are amended to specify that the anti-human gp39 antibodies are non-agonistic of the T cell activation response *in vitro*, and to use the definite article "the" in referring to the purified human $CD4^+$ T cells of the claimed method, for clarity.

Patentability Remarks:

35 U.S.C. §132

The examiner objected to the specification under 35 U.S.C. §132 because the amendment of the response filed March 14, 2006, to correct the error in the description of the P and E mutations on page 33 allegedly introduced new matter into the application, by changing the description of the amino acid sequences of biological materials identified in the application (*see* page 3 of the official action). In a teleconference with the examiner on June 14, 2006, the examiner explained to applicants' representative that this objection pertains to the deposited biological material, and that the examiner is requiring verification that the amendment to correct

the error in the description of the P and E mutations on page 33 does not alter the description of the amino acid sequences of the deposited biological material.

The deposited biological material disclosed in the specification is murine hybridoma IgG1 anti-human CD40 Ligand (gp39) 24-31 having ATCC designation HB 11712, deposited on September 2, 1994. *See* the paragraph providing deposit information that was added to page 67 of the application by the amendment filed September 30, 1994, and the Declaration of Biological Deposit filed April 12, 2005. The description of the P and E mutations on page 33 that was amended by the previous response refers to sequences in a human gamma 4 constant domain (*see* page 33, line 27), which were well-known by persons of skill in the art at the time of filing, whereas the disclosed murine monoclonal anti-gp39 antibody referred to as "24-31" that is produced by the deposited hybridoma is an IgG1 antibody with a murine gamma 1 constant domain. **Therefore, through the undersigned, the applicants submit that the amendment to correct the error in the description of the P and E mutations on page 33 does not refer to or alter the description of the amino acid sequences of the deposited biological material.** Withdrawal of the objection to the specification under 35 U.S.C. §132 is respectfully requested.

35 U.S.C. §112, First Paragraph, Written Description

Claims 2, 3, 5, 16-28, 30, and 33-38 are newly rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description of the claimed invention in the specification. The examiner alleges that the specification does not contain a written description of the step of the claimed method comprising assaying *in vitro* to identify anti-human gp39 antibodies that are non-agonistic of an activation response by purified $CD4^+$ T cells, in compliance with the requirements of 35 U.S.C. §112, first paragraph,

The applicants submit that the claimed invention is clearly described in the application in such a manner as to convey to one of skill in the art that the inventors had possession of the claimed invention at the time of filing. The application notes on page 12, lines 6-19, that goals of the present application are to provide anti-human gp39 antibodies that antagonize the interaction of human gp39 with CD40, bind to the same epitope of human gp39 as murine antibody 24-31, and are non-agonistic of T cell activation, and to provide methods of using such

non-agonistic anti-gp39 antibodies for treatment of human disease conditions that are treatable by modulating gp39 expression and/or inhibiting the interaction of human gp39 with CD40, such as autoimmune diseases, graft-versus-host disease, and transplantation. As described on page 35, lines 10-12, "the inventors discovered surprising properties of the subject anti-human gp39 antibodies, namely that they do not agonize T-cell activation, but still prevent T cell/B cell interaction, based on various in vitro assays." The *in vitro* assays used by the applicants to demonstrate that the anti-human gp39 antibodies of the invention are non-agonistic of T cell activation are described in general terms on page 35, line 12, to page 37, line 29, and in detail in Examples 18-21 on pages 54-57. The *in vitro* assays described on pages 35-37 and in Examples 18-21 to determine if an anti-human gp39 antibody is non-agonistic of T cell activation comprise culturing purified human $CD4^+$ T-cells *in vitro* in the presence of immobilized anti-CD3 antibodies, contacting the $CD4^+$ T-cells with the anti-human gp39 antibody of interest, and measuring T cell proliferation and the production of the cytokines IL-2, IL-4, and IFN- γ. As described in the application, control anti-gp39 antibody TRAP-1 stimulates purified human $CD4^+$ T-cells to proliferate and produce IL-2, IL-4, and IFN- γ in the disclosed *in vitro* assays, whereas an antibody of the claimed invention, IDEC-131, is non-agonistic of these T cell activation responses. IDEC-131 is a humanized anti-human gp39 antibody derived from murine antibody 24-31 (*see* Brams *et al.*, International Immunopharmacology, 2001, 1:277-194, copy attached).

Step (d) of claim 2 is amended to specify the step of assaying *in vitro* to identify soluble anti-human gp39 antibodies that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured with immobilized anti-CD3 antibodies, the activation response selected from the group consisting of T-cell proliferation, the production of interleukin 2 (IL-2), the production of interleukin-4 (IL-4) and the production of interferon γ (IFN- γ). Since the application expressly describes the property of being non-agonistic of T cell activation as one of the surprising properties of the anti-human gp39 antibodies of the disclosed invention, and it describes the *in vitro* assay methods of step (d) of claim 2 as methods by which one can determine if an antibody is non-agonistic of T cell activation, one of skill in the art would reasonably consider the disclosed step of assaying *in vitro* to determine if the anti-human gp39 antibodies are non-agonistic of an activation response to be an inherent and necessary part of the

claimed method comprising identifying anti-human gp39 antibodies are non-agonistic of an activation response. Accordingly, one of skill in the art would reasonably consider that the claimed invention is described in the application in such a manner as to convey to that the inventors had possession of the invention at the time of filing. Withdrawal of the rejection of claims 2, 3, 5, 16-28, 30, and 33-38 under 35 U.S.C. §112, first paragraph, for lack of written description is therefore respectfully requested.

35 U.S.C. §103(a)

Claims 2, 3, 5, 16-28, 30, and 33-39 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable in view of Black *et al.* (U.S. Patent No. 6,001,358), in combination with Schrader *et al.* (U.S. Patent No. 5,627,052), Burkly *et al.* (US2002/0028202 A1), and Wilson *et al.* (U.S. Patent No. 6,372,208 B1), "essentially for the reasons of record," and further in view of Van den Eertwegh *et al.* (1993) and Roy *et al.* (1993). The latter two references are newly added to the statement of the rejection, and the examiner alleges that Van den Eertwegh *et al.* (1993) and Roy *et al.* (1993) "make it clear that the CD40 ligand expressing cells involved in T-B cell interactions were associated and analyzed in the context of IL-2, IL-4, and interferon-γ at the time the invention was made.

The applicants respectfully submit that the claimed invention would not have been obvious under 35 U.S.C. § 103(a) to one of ordinary skill in the art at the time the invention was made, because neither the combination of cited references nor the general knowledge of one of ordinary skill in the art would have provided one of ordinary skill in the art with any suggestion or motivation to perform the claimed method, nor would they have provided one of ordinary skill in the art with a reasonable expectation that the claimed method could be performed successfully.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. The teaching or suggestion to make the claimed combination and the reasonable expectation of

success must both be found in the prior art, not in applicants' disclosure. *See* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), *also* In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) citing In re Raynes, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992), *and* M.P.E.P. § 2142.

To establish a *prima facie* case that the claimed invention was obvious, the prior art or general knowledge of one of ordinary skill in the art must have provided motivation to one of ordinary skill in the art to assay *in vitro* to identify soluble anti-human gp39 antibodies that are non-agonistic of T cell activation responses such as T cell proliferation and the production of the cytokines IL-2, IL-4, and IFN- γ by purified human $CD4^+$ T-cells cultured *in vitro* in the presence of immobilized anti-CD3 antibodies. Furthermore, the teachings of the prior art or the general knowledge of one of ordinary skill in the art must have provided one of ordinary skill in the art with a reasonable expectation that screening soluble anti-human gp39 antibodies for the ability to agonize T cell proliferation and the production of IL-2, IL-4, and IFN- γ by purified human $CD4^+$ T-cells cultured *in vitro* in the presence of immobilized anti-CD3 antibodies would successfully identify anti-human gp39 antibodies that are non-agonistic of said activation responses.

At the time the invention was made, Black *et al.*, either alone or in combination with the cited secondary references, Schrader *et al.*, Burkly *et al.*, Wilson *et al.*, Van den Eertwegh *et al.*, and Roy *et al.*, nor the generally available knowledge, taught or suggested to one of ordinary skill in the art that the binding of soluble anti-human gp39 antibodies to gp39 of purified human $CD4^+$ T-cells cultured *in vitro* in the presence of immobilized anti-CD3 antibodies is capable of agonizing such T cell activation responses as T cell proliferation and the production of the cytokines IL-2, IL-4, and IFN- γ.

Furthermore, Black *et al.*, either alone or in combination with the cited secondary references, nor the generally available knowledge, would have taught or suggested to one of ordinary skill in the art that soluble anti-human gp39 antibodies that antagonize the interaction of human gp39 with CD40 could be screened for the ability to bind to gp39 of purified human $CD4^+$ T-cells cultured *in vitro* in the presence of immobilized anti-CD3 antibodies and agonize T cell

proliferation and the production of the cytokines IL-2, IL-4, and IFN- γ, with the reasonable expectation that anti-human gp39 antibodies could be successfully identified that are non-agonistic of said activation responses.

Black *et al.* discloses anti-human gp39 antibodies that compete for binding to human gp39 with murine antibody 24-31, and therapeutic methods in which such anti-gp39 antibodies are administered to treat multiple sclerosis and other diseases. As noted by the examiner, Black *et al.* teaches that gp39$^+$ T cells produce IL-2, IL-4, and IFN-γ, *citing* the Van den Eertwegh *et al.* (1993) reference that is newly cited in the statement of rejection (*see* col. 4, lines 11-12). The examiner further describes Black *et al.* as teaching methods of treating diseases with antibodies that bind gp39 (CD40 ligand), "which block signals delivered via CD40," *citing* Examples 2, 3, and 11-17 of Black *et al.* (*see* page 7 of the official action). Black *et al.* neither describes nor suggests that signals that affect T cell activity are delivered to the T cells via binding of gp39 to CD40. Examples 2, 3, 12 and 15 of Black *et al.* describe *in vitro* and *in vivo* studies of the effect of anti-gp39 antibodies on B cell proliferation and differentiation (Ig production), and Examples 11, 13, 14, 16, and 17 describe biochemical assays of the ability of the disclosed anti-gp39 antibodies to bind to gp39 and block binding to CD40. The cited examples of Black *et al.*, like the document as a whole, are concerned with the effects on B cells of signals delivered by gp39$^+$ T cells to the B cells via CD40. **Black et al. neither describes nor suggests that signaling through gp39 can modulate an activation response of T-cells *in vivo* or *in vitro* such as T-cell proliferation or the production of a cytokine selected from the group consisting of IFN-γ, IL-4, and IL-2**. In fact, Example 4 of Black *et al.* discloses results that show that anti-gp-39 antibodies **do not** inhibit *in vivo* antigen-specific proliferative responses of human T cells in the spleens of hu-PBL-scid mice, which Black *et al.* states "demonstrate that treatment with anti-gp39 does not result in deletion or functional inactivation of antigen-specific T cells in hu-PBL-scid mice and support the contention that inhibition of TT specific antibody responses by anti-gp39 is due to blockade of gp39-CD40 interactions and subsequent B cell responses rather than T cell inactivation." *See* col. 24, lines 14-20. Black *et al.* further teach that T cell activation and T cell-mediated responses are inhibited by anti-gp39 antibodies *in vivo* because the anti-gp39

antibodies block CD40 signaling in B cells and dendritic cells and interfere with antigen presentation to T cells (*in* col. 32, lines 8-13). It is important to note that by expressly teaching that T cell activity is regulated by multicellular interactions that do not involve direct signaling through gp39, Black *et al.* teaches away from the claimed method that comprises assaying to determine the ability of anti-gp39 antibodies to affect activation responses of purified human T cells *in vitro*.

The examiner acknowledges that Black *et al.* does not describe assaying to identify anti-gp39 antibodies that affect the ability of purified human $CD4^+$ T-cells T cells to proliferate and/or produce cytokines such as IL-2, IL-4, and IFN-γ *in vitro*. The examiner alleges that Black *et al.* and Wilson *et al.* both teach inhibitory anti-gp39 antibodies and their effects on T cell mediated activation and functions, and that in view of the recognized roles of IL-2, IL-4, and IFN-γ in immune responses as described by Black *et al.* and Wilson *et al.*, Van den Eertwegh *et al.*, and Roy *et al.*, it would have been obvious to one of ordinary skill in the art to perform assays of the claimed invention to determine the effects of antagonistic anti-gp39 antibodies on the production of IL-2, IL-4, and IFN-γ and on T cell proliferation *in vitro*, using known methods such as those disclosed by Schrader *et al.* and Burkly *et al.* The examiner further alleges that the strongest rationale for combining the cited references is that one of ordinary skill in the art would have recognized, from a line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would result from the combination. *See* page 6 of the official action.

Schrader *et al.* describes a general method for screening a population of antibody-producing B cells to identify an antibody that has a desired function, such as the ability to mimic an activity of a biologically active factor, *e.g.*, an interleukin, colony stimulating factor, or interferon (*e.g.*, *see* col. 8, lines 38-49).

Burkly *et al.* describes methods of assaying or screening the ability of an antagonist such as an antibody to block a response to a particular cytokine (*e.g.*, *see* pages 7-8 and 13).

Wilson *et al.* teaches that an agent that interferes with the binding of gp39 on T cells to CD40 on B cells prevents the activation of T helper cells *in vivo* (col. 7, lines 5-6), and describes

an assay for detecting the ability of an anti-gp39 antibody to inhibit antigen-stimulation of T cells *in vivo* comprising co-administering the anti-gp39 antibody and a T-cell-stimulating antigen to a mouse, isolating T cells from the treated mouse, and measuring the ability of the isolated T cells to proliferate *in vitro*. Wilson *et al.* show that T-cells isolated from a mouse that has been injected with a T-cell-stimulating antigen are able to proliferate *in vitro*, whereas co-injection of a mouse with both a T-cell-stimulating antigen and the anti-murine gp39 antibody MR1 prevents the isolated T-cells from proliferating. *See* col. 21.

Van den Eertwegh *et al.* (copy attached) describe experiments that show that $gp39^+$ cells and cells that produce IL-2, IL-4, and IFN-γ appear in the spleens of mice with similar kinetics following immunization (*see* pages 1560-61). Using double staining, they also detected $gp39^+$ Th cells that produce IL-2 and/or IL-4 and/or IFN-γ in the spleens of the treated mice (*see* pages 1557), and suggested that after immunization and antigen presentation, T cells with potency to produce IL-2, and/or IL-4, and/or IFN-γ are activated and differentiate *in vivo* into cytokine-producing cells (*see* the paragraph bridging pages 1561-62). As noted above, Black *et al.* also teaches that $gp39^+$ T cells produce IL-2, IL-4, and IFN-γ, *citing* the Van den Eertwegh *et al.* reference. Van den Eertwegh *et al.* thus clarifies that the statement by Black *et al.* that that $gp39^+$ T cells produce IL-2, IL-4, and IFN-γ is based on experimental studies of the activities of $gp39^+$ T cells *in vivo*.

Roy *et al.* (copy attached) describe experiments that show that purified $CD4^+$ T cells that have been cultured in the presence of immobilized anti-CD3 antibody express gp39 (*see* pages 2501-4), and that IL-2, IL-4, and IFN-γ inhibit expression of gp39 by purified $CD4^+$ T cells that are cultured in the presence of immobilized anti-CD3 antibody (*see* page 2501). Black *et al.* also teaches that $CD4^+$ T cells that are cultured in the presence of immobilized anti-CD3 antibody express gp39 (*see* col. 4, first paragraph, cited on page 7 of the official action), so it is unclear how the combination of Roy *et al.* with the previously cited references adds to the motivation of one of ordinary skill in the art to practice the claimed invention with a reasonable expectation of success.

The applicants submit that the combination of Black *et al.* with Schrader *et al.*, Burkly *et al.*, Wilson *et al.*, Van den Eertwegh *et al.*, and Roy *et al.*, would not have provided one of ordinary skill in the art with suggestion or motivation to perform the claimed invention, nor would they have provided a reasonable expectation that the claimed method could be performed successfully. Moreover, the examiner has not shown that a line of reasoning based on established scientific principles would have led one of ordinary skill in the art have to recognize that some advantage or expected beneficial result would result from the alleged combination.

Independent claim 2 is directed to an improved method of treating an autoimmune disease or disorder treatable by inhibiting gp39 expression or the interaction of human gp39 with CD40, which comprises assaying to identify soluble anti-human gp39 antibodies that

(i) inhibit the interaction of human gp39 with CD40,

(ii) compete for binding to human gp39 with murine antibody 24-31, and

(iii) are non-agonistic of an activation response by purified human $CD4^+$ T-cells *in vitro* that have been cultured with immobilized anti-CD3 antibodies, wherein the activation response is selected from the group consisting of T-cell proliferation and the production of a cytokine selected from the group consisting of IFN- γ, IL-4, and IL-2,

and administering a therapeutically effective amount of such anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40, compete with murine antibody 24-31 for binding to human gp39, and are non-agonistic of said human T-cell activation response.

The claimed method thus includes the step of assaying *in vitro* to identify soluble anti-human gp39 antibodies that are non-agonistic of an activation response selected from the group consisting of T-cell proliferation and the production of IL-2, IL-4, and IFN-γ, by purified human $CD4^+$ T-cells that have been cultured with immobilized anti-CD3 antibodies.

As discussed above, Black *et al.* disclose experimental data that suggests that anti-human gp39 antibodies do not directly affect human T cell activation responses (*see* Example 4), and they expressly teach that inhibition of T cell activation and T cell-mediated responses by anti-gp39 antibodies *in vivo* is due to the blocking of CD40 signaling in B cells and dendritic cells,

which interfere with antigen presentation to T cells (*see* col. 32, lines 8-13). The teaching of Wilson *et al.* that an agent that interferes with the binding of gp39 on T cells to CD40 on B cells *in vivo* prevents the activation of T helper cells (col. 7, lines 5-6) would therefore have been understood by one of ordinary skill in the art as an effect that is likely to be due to interference with antigen presentation to T cells by B cells and dendritic cells, as taught by Black *et al.* Accordingly, to the extent that Black *et al.* and Wilson *et al.* suggested assaying the effects of anti-gp39 antibodies on T cell activation responses, one of ordinary skill in the art would reasonably have been motivated by their teachings to use a multicellular assay system that includes B cells and dendritic antigen-presenting cells, such as the *in vivo* assay methods described by Wilson *et al.* and Black *et al.*, rather than to use the *in vitro* assay with purified human $CD4^+$ T-cells of the claimed invention.

As discussed above, Van den Eertwegh *et al.* teach that expression of $gp39^+$ by Th cells *in vivo* following immunization appears to be associated with Th cell activation and differentiation into cells that produce cytokines that include I L-2, IL-4, and IFN-γ, and Roy *et al.* show that purified $CD4^+$ T cells that have been cultured in the presence of immobilized anti-CD3 antibody express gp39. Schrader *et al.* and Burkly *et al.* describe general assay methods for screening antibodies. **At the time the invention was made, neither the combination of cited references nor the general knowledge of one of ordinary skill in the art taught or suggested that activation responses of purified human $CD4^+$ T-cells *in vitro* that have been cultured with immobilized anti-CD3 antibodies, such as T-cell proliferation and the production of IL-2, IL-4, and IFN-γ, can be agonized by the binding of soluble anti-human gp39 antibody to the gp39 antigen of the purified $CD4^+$ T-cells. This is an experimental result that was only disclosed in the present application (*see* Examples 18-20 and Figs. 16, 17, 19, and 20). Therefore, neither the combination of cited references nor the generally available knowledge would have motivated one of ordinary skill in the art at the time the invention was made to practice the claimed method.**

At the time the invention was made, it was not known and could not have been predicted by one of ordinary skill in the art that soluble anti-human gp39 antibodies that bind to gp39 of

purified human $CD4^+$ T-cells cultured *in vitro* in the presence of immobilized anti-CD3 antibodies differ in their ability to agonize T cell activation responses such as T cell proliferation and the production of the cytokines IL-2, IL-4, and IFN- γ, and that it is possible to perform the claimed method to identify soluble anti-human gp39 that are non-agonistic of such T cell activation responses. **Therefore, at the time the invention was made, neither the combination of cited references nor the general knowledge of one of ordinary skill in the art would have taught or suggested to one of ordinary skill in the art that the assay of the claimed invention could be performed with the reasonable expectation that soluble anti-human gp39 antibodies could be successfully identified that are non-agonistic of T cell activation responses by purified human $CD4^+$ T-cells cultured *in vitro* in the presence of immobilized anti-CD3 selected from T-cell proliferation and the production of a cytokine selected from the group consisting of IFN- γ, IL-4, and IL-2.**

As neither the combination of cited references nor the general knowledge of one of ordinary skill in the art would have provided motivation to one of ordinary skill in the art at the time the invention was made to perform the claimed method, or to have a reasonable expectation that the claimed method could be performed successfully, a *prima facie* case of obviousness has not been established. Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as allegedly having been obvious in view of Black *et al.*, Schrader *et al.*, Burkly *et al.*, and Wilson *et al.*, and further in view of Van den Eertwegh *et al.*, and Roy *et al.*, is respectfully requested.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

Date: November 6, 2006

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